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Original Article

Short-Term Efficacy and Safety of Adding Ezetimibe to Current Regimen of Lipid-Lowering Drugs in Human Immunodeficiency Virus-Infected Thai Patients Treated with Protease Inhibitors

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SUMMARY: Long-term complications of protease inhibitor (PI) treatment includes increased cardiovascular risks due to dyslipidemia in patients infected with human immunodeficiency virus (HIV). Ezetimibe reduces low-density lipoprotein cholesterol (LDL-C) without drug interactions with PIs and statins. Furthermore, the addition of ezetimibe to statins is an optional treatment in HIV-infected patients with uncontrolled dyslipidemia. The objective of this study was to determine the short-term efficacy and safety of adding ezetimibe to the currently administered statin regimen. Thirty-two patients received ezetimibe (10 mg daily) in addition to their ongoing lipid-lowering therapy for 18 weeks. Serum LDL-C, total cholesterol (TC), triglycerides (TGs), TC/high-density lipoprotein cholesterol (HDL-C) ratio, and HDL-C were measured at baseline, and weeks 6, 12, and 18. Safety parameters were assessed by adverse event reports and laboratory assessments throughout the study. The mean percent change from baseline to endpoint in LDL-C, TC, TGs, and TC/HDL-C ratio were −23.3% ($p < 0.001$), −15.0% ($p = 0.001$), −22.1% ($p = 0.004$), and −16.2% ($p = 0.018$), respectively. No adverse event or other abnormal laboratory results occurred. Addition of ezetimibe to currently administered lipid-lowering drugs in HIV-infected patients receiving PIs with uncontrolled dyslipidemia demonstrated significantly improved efficacy in reducing their LDL-C, TC, TGs, and TC/HDL-C ratio levels. Moreover, this therapy was safe and well-tolerated.

INTRODUCTION

Long-term use of highly active antiretroviral therapy (HAART) has significantly improved the quality of life, life expectancy, and the survival of patients infected with human immunodeficiency virus (HIV) (1–3). However, HIV-infected patients still have higher mortality rates than the general population, because of non-AIDS related diseases, such as an increased incidence of cardiovascular diseases (CVDs) (4–7). The results of the Data Collection on Adverse Events of Anti-HIV Drugs (DAD) cohort showed that dyslipidemia was associated with an increasing incidence of myocardial infarction and occurred more frequently in patients receiving protease inhibitors (PIs) (4–13). Dyslipidemia is a major, primary risk of atherosclerosis for CVDs such as coronary heart disease, cerebrovascular disease, and peripheral arterial disease. In 2012, 31% of all global deaths could be attributed to CVDs (14).

Evidence-based treatment of hypercholesterolemia from many guidelines recommends statins as a first-choice medication (1,2,15–17). However, there are serious drug interactions between statins and PIs (2,16,18–21), which limit the recommendation of higher doses of statins when dyslipidemia control is not achieved. Ezetimibe, a cholesterol absorption inhibitor, is a new class of lipid-lowering drugs that exhibits fewer drug interactions between other lipid-lowering drugs and PIs (22–27). However, ezetimibe is not currently enlisted in the National List of Essential Medicines of Thailand; therefore, many patients cannot access this drug. Several studies have showed that adding ezetimibe to statins confers favorable efficacy and safety in patients with uncontrolled dyslipidemia (28–37). Furthermore, the addition of ezetimibe may be an alternative treatment to achieving the goal of lipid-lowering therapy in HIV-infected patients with uncontrolled dyslipidemia. Hence, this study reports the results of the first clinical trial in HIV-infected Thai patients to determine the short-term efficacy and safety of adding ezetimibe to the current regimen of lipid-lowering drugs in controlling dyslipidemia in these PI-treated patients.

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MATERIALS AND METHODS

Patients and population: This study was a prospective, open-labeled, one-group, pre-test–post-test, short-term study with an 18 week follow-up.

This study was approved by the Institutional Review Board of the Bamrasnaradura Infectious Diseases Institute (Protocol No.S003h/57). The study participants were adult HIV-infected patients who visited the Bamrasnaradura Infectious Diseases Institute, Ministry of Public Health between September 2014 and December 2015. HIV-infected patients who were receiving stable PIs and with dyslipidemia that was being treated by statins (with or without fibrates) for at least 6 months prior to the study were recruited. Patients who were pregnant or lactating, or exhibited gastrointestinal tract malabsorption, abnormal

hepatic functions (aspartate aminotransferase [AST] or alanine aminotransferase [ALT] elevation of > 3 times the upper normal limit), and renal impairment (chronic kidney disease stage 3–5; estimated glomerular filtration rate [eGFR] < 60 mL/min/1.73 m^2) were excluded. All patients provided written informed consent prior to their enrollment. All eligible patients were administered ezetimibe (10 mg/day) on day 1 in addition to their current lipid-lowering drugs with HAART and were instructed to continue with the ezetimibe treatment until day 126 (week 18). They were also instructed to continue their routine dietary, exercise, and activities. All patients were scheduled to meet the study's researchers at each visit for medication adherence counseling and drug interaction screening.

Data collection: Study visits were scheduled at screening, baseline (week 0), and weeks 6, 12, and 18. Fasting lipid profiles, and biochemistry and hematology data were collected during each visit. CD4 cell counts and plasma HIV-1 viral loads were assessed from their routine treatment workup. Adverse events, including signs and symptoms, were evaluated as safety parameters at every follow-up visit.

Statistical analysis: For statistical assessment, it was estimated that 38 patients would have 95% power to detect a mean difference of low density lipoprotein cholesterol (LDL-C), which would be decreased to 17.3 mg/dL at week 18 from baseline at α-value equal to 0.05 (one-sided). Demographic data were analyzed by descriptive statistics. Repeated-measure analysis of variance (ANOVA) was used to compare the mean difference of LDL-C and other parameters between pre- and post-treatment of each visit to baseline parameters. Data were analyzed using SPSS ver. 18.0 for Windows (SPSS, Chicago, IL, USA). P-values (p) < 0.05 were considered as statistically significant.

RESULTS

A total of 105 patients were screened and met the inclusion criteria, but only 38 patients consented to participate in this study. Thirty-two patients completed the study, while 6 patients withdrew due to inconvenience with the follow-up schedule of the study. Baseline characteristics, including sex, age, body mass index (BMI), duration of exposure to PIs, absolute CD4 cell count, HIV-1 viral load, lipid-lowering drugs, and PI regimens are shown in Tables 1–3.

Efficacy outcome: After 18 weeks, mean (SD) of LDL-C, TC, TGs, and TC/HDL-C ratio were 126.8 (32.7) mg/dL, 202.4 (38.7) mg/dL, 212.7 (81.3) mg/dL, and 3.7 (1.1), respectively. Comparing of the lipid profiles between baseline and week 18 revealed that statistically significant decreases in the mean serum LDL-C, TC, TGs, and TC/HDL-C ratio (all $p < 0.05$). Eighteen (56.2%) patients presented LDL-C levels of < 130 mg/dL. The percent changes of mean serum lipid profiles compared to the baseline value is shown in Fig. 1.

Safety outcome: No patient experienced adverse events (including muscle-related adverse events) or abnormal laboratory parameters during the study period. The safety monitoring parameters are shown in Table 4.

DISCUSSION

As the results of the IMProved Reduction of Outcomes: Vytorin Efficacy International Trial (IMPROVE-IT) study have shown, the combination of ezetimibe and statins have significant benefits in non-HIV-infected patients with acute coronary syndrome (ACS), in the absence of any serious adverse events (31). The IMPROVE-IT study only included patients with ACS and compared the therapeutic

Table 1. Baseline characteristics of patients

Characteristics	Value
women; *n* (%)	19 (59.4)
age; yr, mean (SD)	48.2 (6.7)
BMI; kg/m^2, mean (SD)	22.0 (2.9)
LDL-C; mg/dL, mean (SD)	165.4 (26.8)
duration of exposure to PIs; yr, mean (SD)	8.7 (2.1)
absolute CD4 cell count; cells/μL, mean (SD)	666 (246)
plasma HIV viral load; undetected (< 20 copies/mL), *n* (%)	30 (93.8)

BMI, body mass index; LDL-C, low-density lipoprotein cholesterol; CD4, cluster of differentiation 4; HIV, human immunodeficiency virus.

Table 2. Regimens of lipid-lowering drugs among HIV-infected patients

Lipid-lowering drug	*n* (%)
Statin alone (mg/day)	18 (56.2)
atorvastatin 10	2 (6.2)
atorvastatin 20	10 (31.2)
atorvastatin 40	6 (18.8)
Combination of statins and fibrates	14 (43.8)
statin (mg/day) + fenofibrate (mg/day)	7 (21.9)
atorvastatin 10 + fenofibrate 160	1 (3.1)
atorvastatin 20 + fenofibrate 160	3 (9.4)
atorvastatin 40 + fenofibrate 160	1 (3.1)
atorvastatin 40 + fenofibrate 200	1 (3.1)
rosuvastatin 5 + fenofibrate 160	1 (3.1)
statin (mg/day) + gemfibrozil (mg/day)	7 (21.9)
atorvastatin 10 + gemfibrozil 300	1 (3.1)
atorvastatin 10 + gemfibrozil 600	1 (3.1)
atorvastatin 10 + gemfibrozil 1,200	1 (3.1)
atorvastatin 20 + gemfibrozil 600	3 (9.4)
atorvastatin 40 + gemfibrozil 600	1 (3.1)

Table 3. PIs-based HAART regimens among HIV-infected patients

HAART regimen (PIs-based)	*n* (%)
LPV/RTV	30 (93.8)
2 NRTIs + LPV/RTV	13 (40.6)
NRTI (s) + NNRTI (s) + LPV/RTV	3 (9.4)
NRTI (s) + LPV/RTV	6 (18.8)
NNRTI (s) + LPV/RTV	5 (15.6)
LPV/RTV (mono-therapy)	3 (9.4)
ATV + RTV	2 (6.2)
2 NRTIs + ATV + RTV	1 (3.1)
NNRTI (s) + ATV + RTV	1 (3.1)

PI, protease inhibitor; HAART, highly active antiretroviral therapy; HIV, human immunodeficiency virus; LPV, lopinavir; RTV, ritonavir; NRTI, nucleoside reverse transcriptase inhibitor; NNRTI, non-nucleoside reverse transcriptase inhibitor; ATV, atazanavir.

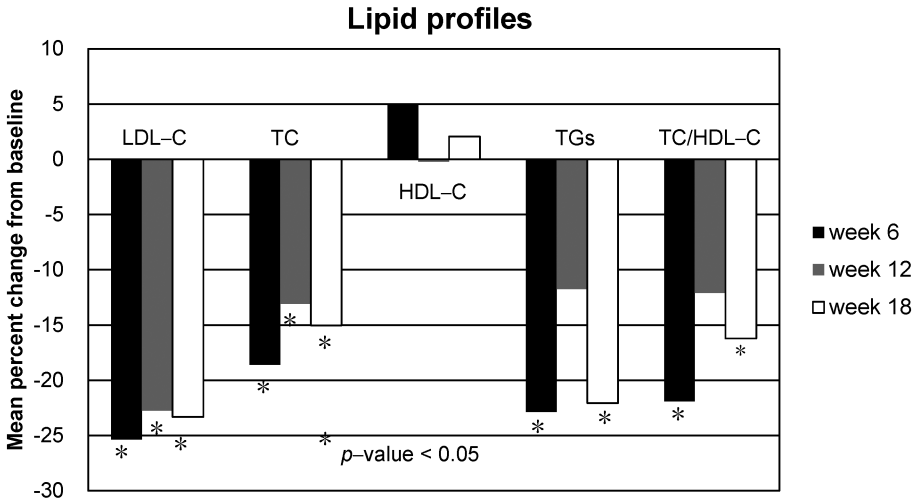

Fig. 1. Mean percent change of lipid profiles from baseline. The mean percent change of lipid profiles from baseline are illustrated. The black, gray, and white color showed the efficacy of lipid profile at week 6, 12, and 18, respectively, which changed for baseline of the study.

Table 4. Laboratory parameters as part of safety monitoring

Parameter (unit, reference range[1)])	Mean (SD)						
	Week 0	Week 6	*p*-value	Week 12	*p*-value	Week 18	*p*-value
Hematology							
WBC ($\times 10^3$/μL, 4.5–8)	7.3 (1.7)	7.5 (1.9)	1.000	7.2 (1.4)	1.000	7.2 (1.7)	1.000
Hb (g/dL, 11–14)	12.9 (1.6)	12.6 (2.6)	1.000	12.7 (1.6)	1.000	12.6 (1.6)	1.000
Hct (% , 35–41)	39.3 (4.2)	39.6 (4.0)	1.000	38.9 (4.5)	1.000	38.4 (4.5)	1.000
Plt ($\times 10^3$/μL, 140–400)	267.6 (64.6)	270.3 (54.8)	1.000	259.2 (61.3)	1.000	265.1 (58.0)	1.000
Renal related parameters							
BUN (mg/dL, 7–20)	12.7 (3.9)	12.4 (3.8)	1.000	12.9 (3.7)	1.000	13.5 (3.5)	1.000
S-Cre (mg/dL, 0.5–0.9)	0.9 (0.7)	0.8 (0.2)	1.000	0.8 (0.2)	1.000	0.8 (0.2)	1.000
Liver function tests							
AST (IU/L, 0–31)	23.1 (5.3)	24.8 (9.5)	1.000	24.5 (6.0)	1.000	23.7 (6.6)	1.000
ALT (IU/L, 0–31)	23.0 (9.9)	24.3 (12.4)	1.000	23.6 (10.1)	1.000	22.3 (8.6)	1.000
ALP (IU/L, 35–104)	76.1 (22.0)	72.4 (22.7)	0.480	75.6 (22.3)	1.000	73.3 (19.8)	1.000

[1)]: Bamrasnaradura Infectious Diseases Institute (BIDI) reference range.
WBC, white blood cell; Hb, hemoglobin; Hct, hematocrit; Plt, platelet; BUN, blood urea nitrogen; S-Cre, serum creatinine; AST, aspartate aminotransferase; ALT, alanine aminotransferase; ALP, alkaline phosphatase.

efficacy in patients administered either 40 mg simvastatin alone or a combination of 40 mg simvastatin plus 10 mg ezetimibe. The difference in the current study was that our study population comprised HIV-infected patients who were receiving PIs and lipid-lowering drugs for uncontrolled dyslipidemia. The prevalence of hypercholesterolemia in Thai HIV-infected patients was high (38). This study showed that the addition of ezetimibe to currently administered therapy significantly decreased LDL-C, TC, TGs, and TC/HDL-C ratio and slightly increased the HDL-C levels in week 18, albeit not significantly. These results are consistent with the results of previous studies (35–37). In the present study, the mean LDL-C reduction observed (38.6 mg/dL, 23.3%) was even lower than that previously reported (17.3–32.0 mg/dL, 7–18%), because our patients had a higher mean baseline LDL-C than that of the previous studies. Despite many patients being treated with atorvastatin (a higher potency statin), the reduction effects on LDL-C might be from a combination with fibrates in our patients. The changes of TGs in this study were statistically significant, which could have been due to 14 patients (43.8%) being treated with a combination with fibrates.

We found no difference between the lopinavir (LPV)/ritonavir (RTV) and atazanavir (ATV) + RTV groups in the outcome of dyslipidemia. However, only 2 patients (6.2%) were administered ATV (boosted with RTV) when compared to the LPV/RTV group ($n = 30$, 93.8%); thus, the former had too small of a sample size to enable a definite conclusion regarding this issue. In contrast, the addition of ezetimibe was beneficial and decreased the LDL-C in both groups. This study found that more than half of the patients (18 patients, 56.2%) achieved the LDL-C goal. There were 11 patients (34.4%) who received statin alone and 7 patients (21.9%) who received combination of statins and fibrate. These results could suggest that most patients had problems with hypercholesterolemia and dyslipidemia because they received moderate to high doses of statins in both groups (statin alone and combination groups).

Additionally, we found that the remaining of 10 patients (31.2%) could possibly achieve the LDL-C goal if they

were treated with the recommended maximum daily dose of statins with or without fibrates. Therefore, the addition of ezetimibe tended to decrease LDL-C and help achieve this goal. On evaluating the safety of this treatment, none of the patients in this study presented with any ezetimibe-related adverse events or laboratory abnormalities. This results little varied when compared to that of previous studies. A prospective, open-label study by Berg-Wolf et al. showed that only 1 patient who experienced asymptomatic elevation of creatine phosphokinase level, which subsequently returned to normal after ezetimibe discontinuation (36). Another randomized, placebo-controlled, crossover study by Chow et al. showed that 5 of 44 patients experienced grade 3 toxicities, including fever ($n = 1$), decreased absolute neutrophil count ($n = 1$), increased total bilirubin ($n = 2$), and nausea/vomiting ($n = 1$). The most common toxicities were ache/pain/discomfort and gastrointestinal symptoms such as nausea, diarrhea, and distention. However, none of the patients experienced a serious ezetimibe-related adverse event and required to discontinue treatment due to drug toxicities from adding ezetimibe to ongoing statin therapy when compared with placebos (37). Thus, the addition of ezetimibe to statins in HIV-infected patients receiving PIs appeared to be safe and well-tolerated (35–37).

There were some limitations to this study. First, this study was a single-center, pre–post study with a small sample size and short-term therapy. Second, patients received only general counseling about lifestyle modification that was not an intensive program for diet control or exercise. Third, patients were treated with a variation on the backbone of HAART and lipid-lowering drugs.

In conclusion, the addition of ezetimibe to the current regimen of lipid-lowering drugs in HIV-infected patients with uncontrolled dyslipidemia receiving PIs, significantly improved short-term efficacy by reducing their LDL-C, TC, TGs, and TC/HDL-C ratio, and was safe and well-tolerated.

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Conflict of interest None to declare.

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